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(71) *Sökande* *Staffan Skogvall, Lund SE*
Applicant (s)

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A. Södervall

Anita Södervall

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PATENT- OCH REGISTRERINGSVERKET
SWEDEN

Postadress/Adress
Box 5055
S-102 42 STOCKHOLM

Telefon/Phone
+46 8 782 25 00
Vx 08-782 25 00

Telex
17978
PATOREG S

Telefax
+46 8 666 02 86
08-666 02 86

Staffan Skogvall
Ansökningsnr
Referens
2991261

MEDICAMENT

Field of the Invention

The present invention relates to the use of a compound having antagonist activity in the manufacture of a medicament for use in therapeutic or prophylactic treatment of a human or animal body, as well as a method of treatment, wherein said compound is administered.

Background of the Invention

Receptors of the 5-HT (serotonin; 3-(β-aminoethyl)-5-hydroxyindole) type are well known, and their relevance has mainly been reported in conjunction with treatment of CNS, muscle and gastric disorders, as disclosed in e.g. WO 98/18458 and US 5 246 935. In such treatments, compounds having agonist activity to a 5-HT_1 receptor are often used.

Receptors of the 5-HT_2-type are well known through *inter alia* US 5 869 497, US 5 705 519 and US 5 246 935. The relevance of receptors of the 5-HT_2-type has been reported in conjunction with e.g. CNS and neuronal disorders. Such disorders are often treated with compounds having antagonist activity to a receptor of the 5-HT_{2A}-, 5-HT_{2B}- or 5-HT_{2C}-type. Examples of such compounds are ritanserin and naftidrofuryl. A review of typical agonists and antagonists of various 5-HT receptors is disclosed in R.A. Glennon, Neuroscience and Biobehavioral Reviews, 14, 35-47 (1990), the whole content of which is incorporated herein by reference. For a review of 5-HT receptors, see Gerhardt, C.C., van Heerikhuizen, H., Eur. *J. Pharm.*, 334, 1-23 (1997), which is also incorporated herein by reference. As examples of other 5-HT receptors, mention can be made of receptors of the 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7 type.

SU 1 701 320 A1 discloses the use of serotonin for treatment of acute asthma attacks. This reference does not suggest any receptor mechanism for serotonin, which

is a compound with both a contracting and a relaxing effect on the airways, as is further discussed herein-below.

Disclosure of the Invention

The present invention is based on the novel finding that 5-HT receptors are of utmost importance in regulating bronchocontraction. In summary, it is disclosed herein that compounds having antagonist activity to a 5-HT_2-receptor, preferably a 5-HT_{2A}-, 5-HT_{2B}- or 5-HT_{2C}-receptor, are suitable agents in the treatment of bronchocontraction disorders.

As used herein, the term bronchocontraction comprises an abnormal increase of the force development of smooth muscles, resulting in a reduced diameter in some or all of the airways of the lungs and/or the extrapulmonary airways. Said expression also comprises reduction of airflow caused by swelling, oedema, plasma extravasation or mucous secretion caused by *e.g.* asthma or any other disorder related thereto.

Accordingly, the present invention, in one of its aspects, relates to the use of a compound having antagonist activity to a 5-HT_2-receptor, preferably a 5-HT_{2A}-, 5-HT_{2B}- or 5-HT_{2C}-receptor, in the manufacture of a medicament for therapeutic or prophylactic treatment of a human or animal body, wherein the medicament is intended for treatment of disorders involving bronchocontraction, such as asthma. Said bronchocontraction may also occur in conjunction with such disorders as *e.g.* emphysema, chronic bronchitis, chronic obstructive pulmonary disease, depression, anorectic or bulimic feeding disorders, anxiety or various psychotic conditions, including schizophrenia.

Especially, said medicament is intended for treatment of asthma and disorders related thereto.

In one embodiment of the use according to the invention, said compound is a nitrogen-containing compound having at least one aromatic ring system. Preferably,

said nitrogen-containing compound is selected from a group of compounds comprising derivatives of thiazole, imidazole, thiophene, aniline, pyridine, pyrrol, oxazole, indan, benzodioxane, benzopyran, quinone and triazole.

In another embodiment of the use according to the invention, said nitrogen-containing compound comprises at least two aromatic ring systems. In this embodiment, said nitrogen-containing compound is preferably selected from a group of compounds comprising derivatives of indole, indazole, indene, naphtalene, benzofuran, quinoline and quinoxaline.

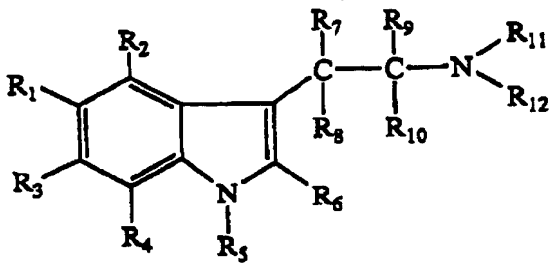
In a preferred embodiment of the present invention, said nitrogen-containing compound is selected from a group comprising ritanserin, naftidrofuryl, ketanserin and pirenperone; or a pharmaceutically acceptable salt thereof.

In yet another embodiment of the use according to the invention, said compound is a peptide or nitrogen-containing non-aromatic cyclic compound. Here, said non-aromatic cyclic compound is preferably selected from a group of compounds comprising derivatives of piperidine, pyrrolidine and piperazine.

In another preferred embodiment (*vide infra* for further details), the present invention relates to the use of a compound having antagonist activity to a 5-HT_2-receptor, preferably a 5-HT_{2A}-, 5-HT_{2B}- or 5-HT_{2C}-receptor, in combination with a compound having agonist activity to at least one of the receptors 5-HT_1, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7 in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction. Subtypes of said 5-HT_1-receptor are 5-HT_{1A}-, 5-HT_{1B}-, 5-HT_{1D}-, 5-HT_{1E}- and 5-HT_{1F}-receptors. In particular, said medicament is intended for treatment of asthma and disorders related thereto.

In this latter embodiment, said compound having antagonist activity to a 5-HT_2-receptor is preferably as defined above. Moreover, said compound having agonist

activity to at least one of the receptors 5-HT_1, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7 is preferably compris d by the general formula I:



(I)

wherein

R_1-R_{12} are independently selected from at least one of a group of substituents (a)-(i) consisting of

(a) H;

(b) OH;

(c) NH_2;

(d) straight chain, branched or cyclic saturated or unsaturated alkyl having 1-6 carbon atoms;

(e) O-alkyl, S-alkyl or N-$(alkyl)_z$, where alkyl is as defined in (d) and z is 1 or 2;

(f) C(O)-alkyl, O-C(O)-alkyl, S-C(O)-alkyl or NH-C(O)-alkyl, where alkyl is as defined in (d);

(g) O-aryl;

(h) F, Cl or Br;

(i) $C(O)R_{13}$, where R_{13} is selected from the groups (b)-(g);

whereby $NR_{11}R_{12}$ optionally together may form a five- or six-membered saturated or unsaturated ring;

or a pharmaceutically acceptable salt thereof.

Most preferably, the substituents R_1-R_{12} are selected from a group comprising

(j) R_1=OCH_3, R_2-R_{12}=H;

(k) R_1=O-n-butyl, R_2-R_{12}=H;

(l) R_1=F, R_2-R_{12}=H;

(m) R_1=OH, R_2=R_3=Cl, R_4-R_{12}=H;

(n) R_1=OH, R_2=R_3=Br, R_4-R_{12}=H;

(o) R_1=OH, R_5=CH_3, R_2-R_4=R_6-R_{12}=H;

(p) R_1=R_7=OH, R_2-R_6=R_8-R_{12}=H;

(q) R_1=R_7=R_8=OH, R_2-R_6=R_9-R_{12}=H;

(r) R_1=OH, R_{11}=CH_3, R_2-R_{10}=R_{12}=H;

(s) R_1=OH, R_{11}=R_{12}=CH_3, R_2-R_{10}=H;

(t) R_1=OH, R_{11}=C(O)CH_3, R_2-R_{10}=R_{12}=H;

(u) R_1=OCH_3, R_2-R_{10}=H, R_{11}=R_{12}=CH_3;

(v) R_1=OH, R_2-R_{12}=H (*i.e.* serotonin);

(x) R_1=C(O)R_{13}, R_2-R_{12}=H.

Most preferably, said compound having agonist activity is 3-(2-aminoethyl)-1H-indole-5-carboxamide or its maleate salt (*i.e.* R_1=$CONH_2$, R_2-R_{12}=H; see *inter alia* US 4 252 803).

As examples of pharmaceutically acceptable salts mention can be made of acid addition salts, *e.g.* a salt formed by reaction with hydrohalogen acids, such as hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid, aliphatic, alicyclic, aromatic or heterocyclic sulphonic or carboxylic acids, such as formic acid, acetic acid, propionic acid, succinic acid, glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, maleic acid, hydroxymaleic acid, pyruvic acid, *p*-hydroxybenzoic acid, embonic acid, methanesulphonic acid, ethanesulphonic acid, hydroxyethanesulphonic acid, halogenbensensulphonic acid, toluenesulphonic acid and naphtalenesulphonic acid.

It should be noted that the medicament prepared according to the present invention may optionally include a combination of two or more of the above outlined compounds.

The typical daily dose of the medicament prepared according to the invention varies within a wide range and will depend on various factors such as the individual requirement of each patient and the route of administration.

Said medicament may be prepared as a composition adapted either for administration via the respiratory

tract or for oral, intravenous, topical, intraperitoneal or subcutaneous administration, in association with one or more pharmaceutically acceptable carriers, diluents or adjuvants that are well known in the art.

Moreover, said medicament is preferably administered via the respiratory tract in the form of *e.g.* an aerosol or an air-suspended fine powder. However, in some cases a useful alternative to administration via the respiratory tract may be oral, topical, parenteral, subcutaneous, transdermal or rectal administration, wherein *e.g.* tablets, capsules, powders, microparticles, granules, syrups, suspensions, solutions, transdermal patches or suppositories are utilised.

The present invention also relates to a method for treatment of disorders involving bronchocontraction, wherein said method comprises administering to a human or animal patient a therapeutically effective amount of a compound having antagonist activity to a 5-HT_2-receptor, especially a 5-HT_{2A}-, 5-HT_{2B}- or 5-HT_{2C}-receptor. Preferably, said method relates to treatment of asthma and disorders related thereto.

In a preferred embodiment of the method according to the present invention, the administered compound may be any one of the compounds set forth above.

In another preferred embodiment, any one of the administered compounds set forth above may be administered in combination with, either simultaneously or sequentially, a compound having agonist activity to at least one of the receptors 5-HT_1, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7. In this embodiment, the agonist compound preferably has the general formula I, as set forth above. Here, the substituents R_1-R_{12} are most preferably selected from the group (j)-(x) outlined above.

Detailed description

The subject matter of the present invention was deduced from animal experiments, where a specific behaviour of the airway smooth muscle called "spontaneous tone" was

examined. The spontaneous tone, which involves a spontaneous continuous contraction in the airway smooth muscle, was studied due to a suspicion that defective regulation of the spontaneous tone could be an important cause of the bronchoconstriction observed in asthmatic patients.

The examinations of the spontaneous tone were performed in accordance with the methods disclosed in the thesis "*Regulation of spontaneous tone in guinea pig trachea*" by S.Skogvall, Department of Physiological Sciences, Lund University, 1999, which is incorporated herein by reference. As was evidenced from these examinations, the airways normally display a highly regular type of oscillating tone if exposed to physiological conditions, and the oscillating tone can be reversibly affected by administration of various substances. When the epithelium is removed, the preparations instead display a strong, smooth type of tone.

In short, the animal experiments in said thesis showed that the spontaneous tone to a large degree is controlled by a powerful regulating factor released from neuroepithelial endocrine (NEE) cells.

Later experiments, not included in the thesis, have revealed that said regulating factor was serotonin, which exerts agonist action on the receptors 5-HT_1, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7 as well as on 5-HT_2-receptors.

Additional experiments have shown that when 1 µM of serotonin was added to denuded airway smooth muscle preparations displaying a strong, smooth spontaneous tone, the average force level was increased significantly, *i.e.* a contraction was observed. A contractile effect of serotonin on airway smooth muscle has been reported in *e.g.* Skogvall, S., Korsgren, M., Grampp, W., *J. Appl. Phys.*, 86:789-798, 1999. However, when 10 µM of serotonin was added, the spontaneous tone was strongly suppressed to a level of around half the force observed in control (drug-fre) conditions. The

spontaneous tone returned to around its normal level when the preparations were again exposed to control conditions. Thus, it has now surprisingly been shown that serotonin brings about contraction of the airways at low concentrations and relaxation at high concentrations, consequently having a dual effect on the airways.

Although SU 1 701 320 corroborates the importance of serotonin for control of airway caliber, the above mentioned dual effect makes serotonin itself unsuitable for treatment of asthma. Indeed, during an acute asthma attack, many small bronchi become partially or completely occluded as a result of mucous formation and/or smooth muscle contraction, which makes it difficult to reach the high concentrations of serotonin necessary for eliciting a relaxing response in these parts of the lung. Thus, administration of serotonin itself involves a considerable risk of contracting small bronchi even further, whereby the asthma attack is aggravated.

In summary, it has now been discovered that agonist action on at least one of the receptors 5-HT_1, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7 results in a relaxing effect, whereas agonist action on 5-HT_2-receptors results in a contractile effect. Conclusively, the dual effect of serotonin is most likely a result of its agonist action on the relaxing 5-HT_1-, 5-HT_4-, 5-HT_5-, 5-HT_6- and 5-HT_7-receptors as well as on the contracting 5-HT_2-receptor. The experiments also indicated that the agonist binding strength of serotonin to a 5-HT_1-, 5-HT_4-, 5-HT_5-, 5-HT_6- or 5-HT_7-receptor is much weaker than its binding strength to a 5-HT_2-receptor.

From these experiments it was perceived that compounds having antagonist activity to a 5-HT_2-receptor are useful as agents for treatment of bronchocontraction disorders, since they are capable of blocking the contractile effect of a compound having agonist activity to a 5-HT_2-receptor. The compounds used according to the present invention may even be administered together with

serotonin; or with any other substanc having agonist activity to a 5-HT_2-receptor as well as to a 5-HT_1-, 5-HT_4-, 5-HT_5-, 5-HT_6- or 5-HT_7-receptor.

Said administration can be simultaneous or sequential, and a powerful relaxing effect on bronchi can be achieved in this manner. Thus, the present invention also relates to the combined use of a compound having antagonist activity to a 5-HT_2-receptor and a compound having agonist activity to at least one of the receptors 5-HT_1, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7 in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction.

CLAIMS

1. Use of a compound having antagonist activity to a 5-HT_2-receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction.

2. Use according to claim 1, wherein the medicament is intended for treatment of asthma and disorders related thereto.

3. Use according to claim 1, wherein said disorder involving bronchocontraction is emphysema, chronic bronchitis, chronic obstructive pulmonary disease, depression, anorectic or bulimic feeding disorders, anxiety or various psychotic conditions.

4. Use according to any one of claims 1-3, wherein said compound is a nitrogen-containing compound having at least one aromatic ring system.

5. Use according to claim 4, wherein said nitrogen-containing compound is selected from a group of compounds comprising derivatives of thiazole, imidazole, thiophene, aniline, pyridine, pyrrol, oxazole, indan, benzodioxane, benzopyran, quinone and triazole.

6. Use according to claim 4, wherein said nitrogen-containing compound is having at least two aromatic ring systems.

7. Use according to claim 6, wherein said nitrogen-containing compound is selected from a group of compounds comprising derivatives of indole, indazole, indene, naphtalene, benzofuran, quinoline and quinoxaline.

8. Use according to claim 6, wherein said compound is selected from a group comprising ritanserin, naftidrofuryl, ketanserin and pirenperone; or a pharmaceutically acceptable salt thereof.

9. Use according to any one of claims 1-3, wherein said compound is a peptide or nitrogen-containing non-aromatic cyclic compound.

10. Use according to claim 9, wherein said non-aromatic cyclic compound is selected from a group of compounds comprising derivatives of piperidine, pyrrolidine and piperazine.

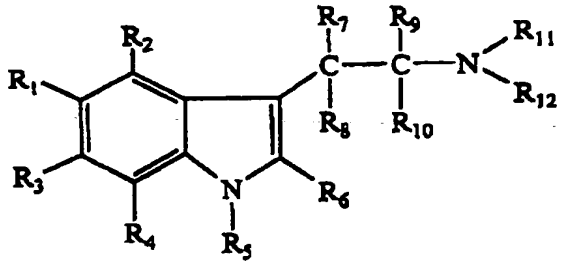
11. Use of a compound having antagonist activity to a 5-HT_2-receptor in combination with a compound having agonist activity to at least one of the receptors 5-HT_1, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7 in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction.

12. Use according to claim 11, wherein the medicament is intended for treatment of asthma and disorders related thereto.

13. Use according to claim 11, wherein said disorder involving bronchocontraction is emphysema, chronic bronchitis, chronic obstructive pulmonary disease, depression, anorectic or bulimic feeding disorders, anxiety or various psychotic conditions.

14. Use according to any one of claims 11-13, wherein said compound having antagonist activity to a 5-HT_2-receptor is as defined in any one of claims 4-10.

15. Use according to any one of claims 11-14, wherein said compound having agonist activity to at least one of the receptors 5-HT_1, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7 is comprised by the general formula I:



(I)

wherein

R_1-R_{12} are independently selected from at least one of a group of substituents (a)-(i) consisting of

(a) H;

(b) OH;

(c) NH_2;

(d) straight chain, branched or cyclic saturated or unsaturated alkyl having 1-6 carbon atoms;

(e) O-alkyl, S-alkyl or N-$(alkyl)_z$, where alkyl is as defined in (d) and z is 1 or 2;

(f) C(O)-alkyl, O-C(O)-alkyl, S-C(O)-alkyl or NH-C(O)-alkyl, where alkyl is as defined in (d);

(g) O-aryl;

(h) F, Cl or Br;

(i) $C(O)R_{13}$, where R_{13} is selected from the groups (b)-(g);

whereby $NR_{11}R_{12}$ optionally together may form a five- or six-membered saturated or unsaturated ring;

or a pharmaceutically acceptable salt thereof.

16. Use according to claim 15, wherein the substituents R_1-R_{12} are selected from a group comprising

(j) R_1=OCH_3, R_2-R_{12}=H;

(k) R_1=O-n-butyl, R_2-R_{12}=H;

(l) R_1=F, R_2-R_{12}=H;

(m) R_1=OH, R_2=R_3=Cl, R_4-R_{12}=H;

(n) R_1=OH, R_2=R_3=Br, R_4-R_{12}=H;

(o) R_1=OH, R_5=CH_3, R_2-R_4=R_6-R_{12}=H;

(p) R_1=R_7=OH, R_2-R_6=R_8-R_{12}=H;

(q) R_1=R_7=R_8=OH, R_2-R_6=R_9-R_{12}=H;

(r) R_1=OH, R_{11}=CH_3, R_2-R_{10}=R_{12}=H;

(s) R_1=OH, R_{11}=R_{12}=CH_3, R_2-R_{10}=H;

(t) R_1=OH, R_{11}=$C(O)CH_3$, R_2-R_{10}=R_{12}=H;

(u) R_1=OCH_3, R_2-R_{10}=H, R_{11}=R_{12}=CH_3;

(v) R_1=OH, R_2-R_{12}=H;

(x) R_1=$C(O)R_{13}$, R_2-R_{12}=H.

17. Use according to claim 15 or 16, wherein said compound having agonist activity is 3-(2-aminoethyl)-1H-indole-5-carboxamide or a maleate salt thereof.

18. A method for treatment of disorders involving bronchocontraction, wherein said method comprises ad-

minist ring to a human or animal patient a therapeutically effective amount of a compound having antagonist activity to a 5-HT_2-receptor.

19. A method for treatment according to claim 18, wherein said disorder involving bronchocontraction is emphysema, chronic bronchitis, chronic obstructive pulmonary disease, depression, anorectic or bulimic feeding disorders, anxiety or various psychotic conditions.

20. A method for treatment of asthma and disorders related thereto, wherein said method comprises administering to a human or animal patient a therapeutically effective amount of a compound having antagonist activity to a 5-HT_2-receptor.

21. A method according to any one of claims 18-20, wherein said compound is as defined in any one of claims 4-10.

22. A method according to any one of claims 18-21, wherein said compound is administered in combination with, either simultaneously or sequentially, a compound having agonist activity to at least one of the receptors 5-HT_1, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7.

23. A method according to claim 22, wherein said compound having agonist activity to at least one of the receptors 5-HT_1, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7 is as defined in any one of claims 15-17.

ABSTRACT

The present invention relates to the use of a compound having antagonist activity to a 5-HT_2-receptor in the manufacture of a medicament for use in therapeutic or prophylactic treatment of a human or animal body, wherein the medicament is intended for treatment of disorders involving bronchocontraction, such as asthma. The present invention also relates to a method for treatment of disorders involving bronchocontraction, wherein a therapeutically effective amount of a compound having antagonist activity to a 5-HT_2-receptor is administered to a human or animal patient.